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Systemic Inflammation in Lewy Body Diseases: A Systematic Review

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Abstract

Objective

Few studies have investigated the role of inflammation in Lewy Body Dementia (LBD) and variable results have been found. We systematically reviewed the literature for evidence of systemic inflammatory changes in Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD). Due to the low number of studies we also included Parkinson's disease (PD).

Methods

Key terms were used to search the relevant databases. Titles and abstracts were screened and potentially relevant articles were reviewed in full. References of included studies and relevant reviews were searched.

Results

The database search returned 2166 results, 46 of which were finally included in the systematic review. These studies showed a general increase in inflammatory markers in the peripheral blood, most notably interleukin-1beta, tumor necrosis factor-alpha, interleukin-6 and interleukin-10. Studies examining cerebrospinal fluid (CSF) found interleukin-1beta, interleukin-6 and transforming growth factor-beta1 to be particularly increased, and interferon-gamma decreased. C-reactive protein levels were increased, particularly in PDD.

Conclusions

These results provide evidence that LBD is associated with an increased inflammatory response. Furthermore, there may be a stronger general inflammatory response in LBD than in PD, whilst complex changes occur in the individual cytokines.

Keywords: Lewy Body Dementia, Parkinson's Disease, Inflammation, Cytokines, Systematic review

Introduction

The Lewy body dementias (LBD) are amongst the most common causes of dementia, second only to Alzheimer's disease. LBD includes dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), two closely related but clinically distinct causes of dementia. DLB describes dementia that occurs before or within 1 year of Parkinson's disease, and is characterised by fluctuating cognitive function, visual hallucinations and parkinsonism[1]. PDD is dementia occurring in the context of established Parkinson's disease[2].

Although the aetiology of LBD is not clear, it seems likely that inflammation plays a role in the pathogenesis of the disease. There is extensive evidence to support the role for chronic inflammation in Alzheimer's disease (AD) in animal studies and postmortem studies of the brain[3] and in studies of peripheral biofluids[4]. There have been far fewer investigations of the role of inflammation in LBD, however because inflammation seems to be important in dementias such as Alzheimer's disease, it may also have a role in LBD. For example, it has been shown that Interleukin (IL)-6 is correlated with both cognitive decline[5] and poorer baseline function in patients with DLB, and furthermore Tumor Necrosis Factor (TNF)-alpha appears to be associated with an increase in neuropsychiatric features[6]. A longitudinal study of Parkinson's disease patients found that a higher level of IL-6 was associated with an increased risk of Parkinson's disease 4 years later[7], and chronic use of non-steroidal anti-inflammatory drugs has been found to reduce the risk of PD by around 45 %[8]. This evidence strongly supports the theory for an inflammatory component in the pathogenesis of both LBD and Parkinson's disease (PD).

Cytokines are large soluble proteins which act to communicate with immune cells and coordinate inflammatory responses, and are commonly used in studies as markers of inflammation. Furthermore, CRP is a common clinical marker of inflammation. Therefore we conducted a systematic review of the literature for evidence of systemic inflammation by way of raised cytokine and C-reactive Protein (CRP) levels in DLB and PDD. However, due to the low numbers of studies available we also included PD patients as this encompassed a wider array of studies, and provided more information about inflammation in Lewy body diseases.

Methods

Search Strategy

We used the databases MEDLINE, EMBASE and PsycINFO to search for all relevant papers, up to and including 26th August 2016. Key terms used for the search were:

- Lewy body OR lewy bodies OR Parkinson's disease AND
- Inflammation OR inflammatory OR cytokines OR biomarkers AND
- Systemic OR peripheral OR serum OR blood OR CSF OR cerebrospinal fluid

Search criteria was specified to human studies only. Titles and abstracts were screened and potentially relevant articles were reviewed in full. References of included studies and relevant reviews were also searched to ensure all relevant studies were included.

Included Studies

Original studies measuring cytokine concentration in living patients who had been given a formal diagnosis of either Parkinson's disease, Parkinson's disease dementia or dementia with Lewy bodies were included. Studies must have had a comparison healthy control group of subjects without any signs or symptoms of Lewy body disease. We only included studies investigating levels of cytokines and CRP in serum, plasma or CSF and all other markers of inflammation were excluded from our search. Studies measuring cytokine levels from peripheral blood and cerebrospinal fluid (CSF) were reviewed separately, as were those measuring cytokines from patients with Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies. Animal studies, non-English literature and post-mortem studies were not included.

Data extraction

Data was extracted from all included papers and entered into an excel spreadsheet. Information was collected relating to participant demographics, cytokines measured, study design, inclusion and exclusion criteria and key findings.

Results

Literature Search Findings

The initial search yielded 3054 studies from the three databases. There were 888 duplicate studies, leaving 2166 results after these duplicates had been removed. From screening titles and abstracts 2079 studies were excluded. This left 87 articles for review. Excluded articles were mainly review articles or book chapters, imaging studies, postmortem studies, different inflammatory makers, and remaining animal and duplicate studies which had been missed by the database filter.

87 full text articles were reviewed and 49 of these were excluded. Excluded articles mainly comprised of conference articles, studies with no control group, studies not measuring cytokines, and studies not written in English. A total of 38 studies were suitable for the systematic review. Hand-searching included references and relevant reviews yielded a further 8 papers which were suitable, leading to a total of 46 included studies. See figure 1 for summary.

Demographics

The patient populations in the studies were variable and sample sizes were highly variable, with the largest study consisting of 435 patients[9] and the smallest consisting of just 8 patients[10]. The age of the patients varied by almost 30 years, with the youngest patients 48 (+/- 8.3)[11], and the oldest 76 (+/-5)[12]. Disease duration also varied significantly, ranging from de novo disease patients[9,10,13-15] to patients with a mean disease duration of 15.8 (+/- 6.5) years[16]. Medications taken by patients were again variable; the maximum mean amount of levodopa usage was 1072.67 (+/-552.69) mg[17], whilst in some studies no medications were being used by any of the patients[9,18-20].

Patients with PD were investigated in 44 of the 46 studies. Dementia with Lewy Bodies was investigated in 2 studies, PDD was investigated in 4 studies and PD with mild cognitive impairment (PD-MCI) was investigated in one study. The patients with PDD and DLB were on average older than the PD patients.

30 studies investigated cytokine levels in peripheral blood, 10 studies measured cytokine levels in CSF, and 6 additional studies were measuring both peripheral blood and CSF. Studies measuring CRP levels included 10 peripheral blood studies and 1 CSF study. 8 of these studies were measuring CRP alone and the other three were also measuring cytokines. The two studies by Rentzos[21,22] were classified together, as were two of the studies by Mogi[23,24] as the same cohort of patients and controls was used for both of these sets of studies.

Peripheral blood studies

Of the studies investigating cytokine levels in peripheral blood, 23 were using serum samples[10-13,16,17,21,22,25-40] and and 4 used plasma samples[14,18,41,42]. There were no noticeable differences between the findings from the serum and plasma samples, so these were grouped together as 'peripheral blood. All peripheral blood studies used Parkinson's disease for their patient group and none investigated patients with DLB, PDD or PD-MCI.

Of the peripheral blood studies, there was a general overall increase in cytokine levels in patients with PD, with IL-1beta, TNF-alpha, IL-6 and IL-10 showing the largest overall increase. However almost equal numbers of studies found non-significant differences in each of these cytokines. There was an overall increase in pro inflammatory markers IL-2, IL-12 and IL-15 and the anti-inflammatory marker IL-4, though a large proportion of the studies investigating these cytokines also found no significant difference between patients and controls. The only cytokine to show a slight overall decrease in peripheral blood in patients compared to controls was IL-8. Table 1 shows results of all cytokines that were measured in more than one study.

Only one study investigated peripheral blood cytokine levels in LBD, and found no significant difference in levels of IL-12, IL-10, INF-gamma or transforming growth factor (TGF)-beta1 in the 10 PDD patients in their cohort compared to controls[28].

In addition to table 1, Brockmann found no significant difference in levels of IL-16, however there was a significant difference in IL-18 levels in the male Leucine-rich repeat kinase 2 (LRRK2) group, but not the idiopathic parkinson's disease group[37].

Cerebrospinal fluid samples

Of the 14 studies investigating CSF, 12 were investigating patients with Parkinson's disease[10,13,16,18,23,24,35,36,43-47]. Three of these studies also investigated patients with PDD[16,45,46], one of which further included PD-MCI patients[45]. Two studies investigated patients with DLB only[48,49]. Two studies were using ventricular CSF as their biofluid which was collected prior to stereotaxic surgery[23,24] and these two studies were grouped together as they used the same cohort of participants. All other studies used lumbar CSF as their biofluid.

In the CSF some cytokines showed a general increase, whilst others decreased. Apart from one study in which IL-1beta could not be detected, IL-1beta was increased in all studies, though this was only significant in 5 of the studies. TGF-Beta1 was significantly increased in patients in both of the study investigating it. INF-gamma was decreased patients compared to controls, and varying results were found in studies investigating TNF-alpha, with the majority of studies finding no significant differences between patients and controls. IL-2 was only investigated in 2 studies, only one of which found a significant difference. IL-4 only appeared in one study which found no significant difference. Results of all cytokines which were measured in more than one study of CSF are presented in table 2. Also included are cytokines only measured in one CSF study if they had also been measured in peripheral blood to allow comparisons to be made.

In LBD, increased IL-8 appeared to be associated with PDD, and lower levels of IL-6 was associated with DLB. Increased IL-6 and IL-1beta and lower levels of TNF-alpha was associated with PD-MCI.

Some studies also investigated cytokines that had not been investigated in any other studies, and therefore the results of these were not presented in table 2. Martin de Pablos found no significant difference in TGF-Beta2 levels[47], and Mogi found no difference in TGF-alpha levels[24], whilst both found an increase in TGF-beta1 levels. Furthermore, Choi found no significant differences between patients and controls in IL-5, IL-7 or IL-13[10].

CRP levels

Of the 11 studies investigating CRP only one study used CSF[16], and all others measured CRP in peripheral blood[9,15,19,20,39,50-54]. All studies were investigating CRP levels in patients with PD, and two studies also investigated PDD patients.

In general these studies found an increase in CRP levels in patients in comparison to controls, with 7 finding a significant increase. Having a diagnosis of PDD also appeared to be associated with raised CRP levels. One study found significantly higher CRP levels in PDD patients but not in PD patients[16], and the other found a significant increase in both patient groups compared to controls, but a larger increase in PDD patients than in PD patients[15]. In addition, a study which found significantly higher levels of CRP in PD patients who experience hallucinations found that this sub-set of patients also had a lower MMSE score, which may further be correlated to the higher CRP levels[52]. These studies therefore imply that there may be an association between CRP levels and PD progressing to PDD.

Discussion

We reviewed the literature for evidence of systemic inflammation in PD and LBD, specifically looking at studies of cytokine levels as a commonly used marker of inflammation in research, and CRP levels as a common clinical marker of inflammation. We found a general increase in cytokines in the peripheral blood and in the CSF, with cytokines such as IL-1beta, IL-6, TNF-alpha and IL-10 being particularly increased in the peripheral blood, and IL-1beta, IL-6 and TGF-beta1 being particularly increased in the CSF. In the peripheral blood, there were no cytokines which were consistently decreased, whilst in the CSF INF-gamma was decreased in both studies. CRP levels were generally increased in patients with PD and PDD. Therefore, we found that overall there is an increased inflammatory response in patients with LBD and PD.

LBD had an increased inflammatory response compared to PD, with PDD patients having higher levels of CRP in blood and in CSF. Previously, increased CRP levels have been associated with dementia[55] and CRP has been correlated with cognitive deterioration in patients with MCI[56], making it likely that increased CRP levels may correlate with cognitive decline. However, more complex changes appear to occur in individual cytokines in LBD; IL-1beta was increased in patients with PD-MCI[45], and was also inversely correlated with MMSE scores in PD patients[34] something which is also found in other types of dementia[57]. However, there was no significant difference in IL-1beta levels in DLB. Furthermore IL-6 was decreased in the DLB study[49], whilst being increased in PD-MCI[45]. These findings suggest that the levels of cognitive impairment and parkinsonism combined may impact on the role that each individual cytokine plays in the disease pathogenesis.

The most commonly studied cytokines were the pro-inflammatory cytokines TNF-alpha, IL-1beta and IL-6. Studies have also reported increased levels of these cytokines in the brain in PD patients, suggesting that they are likely to be playing a role in the neuroinflammatory processes[43,58-60]. IL-1beta was the most consistently increased cytokine. In all peripheral blood and CSF studies whereby IL-1beta could be detected an increase was found, and the studies which found non-significant increases tended to have high standard deviation. IL-1 has potent effects on the brain both systemically whereby it induces sickness behaviour[61] and in the CNS, where it has been implicated in both acute brain injury[62], and chronic neurodegeneration, particularly in AD[63]. Furthermore, LPS-mediated IL-1beta elevation has been shown to potentiate the amount of DA neuronal loss in rats[64]. From the evidence

gathered in this systematic review, it is likely that IL-1 is playing a role in the pathogenesis of PD and LBD.

IL-6 is involved in inducing acute phase reactions, and has been the most commonly studied cytokine in PD and LBD. IL-6 has opposing properties; when up-regulated by IL-1beta and TNF-alpha IL-6 has a pro-inflammatory role, precipitating neuronal degeneration and cell death[65]. When IL-6 induces the IL-1 receptor antagonist and IL-10, this triggers neuronal survival[66,67]. Generally there was an increase in IL-6 in peripheral blood and CSF, though many studies found no significant difference. As IL-6 acts as both a pro-inflammatory and anti-inflammatory cytokine its role in PD may change with disease progression, age or with L-Dopa use.

TNF-alpha is also involved in acute phase reactions, and plays a key role in several autoimmune diseases, with TNF-alpha inhibitors being used in the management of conditions such as rheumatoid arthritis, alkalising spondylitis, psoriasis and inflammatory bowel disease. In the studies reviewed, levels of TNF-alpha tended to be increased, however a study of PD-MCI patients found decreased levels of TNF-alpha in the CSF, which may be a compensatory mechanism to prevent deterioration to PDD[45]. It is plausible therefore TNF-alpha may be implicated in the progression from PD towards PDD.

The anti-inflammatory cytokine IL-10 was also consistently raised in the periphery of patients with PD, being significantly increased in most cases, which may be a compensatory mechanism in response to high levels of pro-inflammatory cytokines[21,22,37]. IL-10 was not measured in the CSF, however TGF-beta1 was consistently increased in the CSF which correlated with UDPRS motor score. As TGF-beta has pro- and anti-inflammatory properties, it may be that that TGF-beta1 is acting in a pro-inflammatory manner to worsen disease progression, or it may be acting to compensate for worsening disease[47].

Other factors influencing inflammatory markers

It is evident from these studies that even when using similar methods and diagnostic criteria there is wide variation in results, likely due to individual differences impacting on cytokine levels. For example, cytokines have been found to vary depending on age, with increased inflammatory markers playing a role in ageing and mortality in healthy elderly individuals[68], and associations being found between age and TNF-alpha, IL-6[25], the soluble TNF-alpha receptor1[69], IL-1beta[27] and CRP levels[70]. Age of onset of disease may have an impact on cytokine variation; one study found higher levels of cytokines in juvenile PD than in late

onset PD, suggesting that a more intense inflammatory reaction may result in earlier PD symptoms[24]. Gender may affect baseline cytokine profile, with increased pro-inflammatory cytokine mRNA expression being found in the striatum of male mice compared to females[71]. In humans, males have a more pronounced response to inflammation than women[72]. In PD patients, Brockmann found that whilst males had a higher level of the pro inflammatory cytokine TNF-alpha and IL-6, females had higher levels of IL-4 and IL-12p40, implying that gender may indeed lead to variation in cytokine levels[37].

Medication and disease severity have also been associated with variation in cytokine profiles. Gangemi found that only patients who were being treated with Levodopa had increased levels of cytokines[26], and a study of PBMC found that levodopa was able to enhance IL-6 and TNF-alpha secretion[73], suggesting that the actions of levodopa are in part immuno-modulatory. It may however be that these findings are a result of increased disease severity in patients taking levodopa, as studies have found that worse motor symptoms correlate with IL-6 and TNF-alpha[39,42]. However, Muller found an inverse correlation between IL-6 and motor symptoms[44] and Selikhova found that IL-6 correlated with faster progressing disease[41], suggesting that there are more complex cytokine interactions at play.

Therefore it seems likely that many factors affect baseline cytokine levels, and this may in part explain the variable results found between studies. Neuroinflammation is a complex network of cytokine interactions, something which is likely to vary depending on the health and demographics of the individual. Therefore this must be taken into consideration when studying cytokines in disease.

Mechanisms of systemic inflammation and its effect on neuroinflammation in PD

The importance of this systemic pro-inflammatory response and the impact that it has in PD and LBD has been investigated. It has been suggested that a systemic immune event may precede clinical parkinsonism, allowing a pathogenic stimulus to PD to take advantage[25]. Constipation often precedes a diagnosis of PD[74], and many PD patients have small bowel bacterial overgrowth on presentation[75] suggesting the GI tract might be the source of the inflammation. Prenatal inflammation in rats can lead to an altered inflammatory response and a progressive loss of dopaminergic neurones, suggesting that prenatal infections may be a risk factor for later PD[76].

Peripheral Blood Mononuclear Cells (PBMC) have been studied as a potential cause of the exaggerated inflammatory profile in patients with PD. Studies have found impaired production of IL-2 by PBMCs[73,77], whilst over-production of others has been found[78,79], suggesting that dysregulation in PBMCs may play a role in the altered inflammatory profile.

Theories as to how systemically elevated cytokine levels are able to interact with the CNS have been suggested. Possible mechanisms include communication via the vagus nerve to the nucleus of the solitary tract[80,81], direct communication with macrophages in the circumventricular organs [82], and communication via endothelial cells lining the BBB[83]. Through these pathways, peripheral cytokines may have the ability to communicate with the CNS to induce or potentiate the neuroinflammation seen in PD.

Clinical importance

Clinically, the findings from these studies are likely to be important in optimising management in PD and LBD by focussing on the inflammatory aspect of the disease pathology. Animal studies have investigated the effects of non-steroidal anti-inflammatory drugs (NSAIDs) in models of PD, and aspirin, ibuprofen and COX-2 selective inhibitors have been repeatedly shown to exert neuroprotective effects[84]. Dexamethasone treatment has been found to diminish neuronal damage following MPTP administration[85] and minocycline has been shown to prevent MPTP-induced microglial activation and decrease the production of inflammatory cytokines in mouse models of PD[86].

In human studies, Chen found that regular use of NSAIDs reduces the risk of Parkinson's disease by about 45%[8], with a dose-dependent risk reduction with ibuprofen use[87]. A systematic review showed that non-aspirin, non-steroidal anti-inflammatory drug use is associated with a 15% reduction in risk of PD, which is increased to 29% reduction with regular use[88]. Currently, no studies have investigated the use of NSAIDs as a treatment of established PD. Again in AD, observational studies have found that NSAID use reduces the risk of later AD[89], however clinical trails investigating the use of NSAIDs in dementias such as AD have yielded disappointing results. A systematic review including seven clinical trials found that there was no difference in cognitive decline with NSAIDs compared to placebo[90]. These findings indicate that any benefits of using NSAIDs in AD, and likely also in PD and LBD may be early in disease pathogenesis, possibly at the pre-symptomatic stage.

Currently, the use of anti-inflammatory medications to reduce the risk of PD is limited due to the difficulty in predicting PD cases. Further research into establishing the effect of using anti-inflammatory medications in patients with established disease is needed.

Limitations

There are several limitations to this study which must be taken into account. Firstly, the literature search was limited to cytokines and CRP, therefore studies involving chemokines, inflammatory proteins, soluble inflammatory receptors and other inflammatory molecules were excluded from the search criteria. Furthermore, the biofluid in the search was limited to plasma, serum and CSF. Studies stimulating PBMC were excluded, as were any studies looking at cytokine levels in the brain. Further work should be undertaken to review the literature in respect to these factors.

Methodology was another limiting factor in this study. Whilst the majority of the studies used ELISA to analyse biofluids, other techniques included cytometric bead array, MSD and luminex. This variation in methodology may have led to differences in results obtained.

Conclusions

This systematic review suggests that there is a pro-inflammatory response in the CSF and the peripheral blood in patients with PD and LBD, and furthermore that increased inflammation appears to be correlated with progression of PD towards PDD. In particular, IL-1beta was consistently increased across all studies, making it likely that it is playing a key role in disease progression. It is however it is evident that there is a lack of studies investigating systemic inflammation in LBD, particularly in peripheral blood, and therefore there is a need for further research to investigate this. The information obtained in this review is of high clinical value as it suggests that anti-inflammatory medication may be useful in management of LBD, and although studies have found a correlation between anti-inflammatory medication use and increased risk of Parkinson’ s disease, there is a need for further work to investigate the use of anti-inflammatory medication in established LBD.

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Figure 1

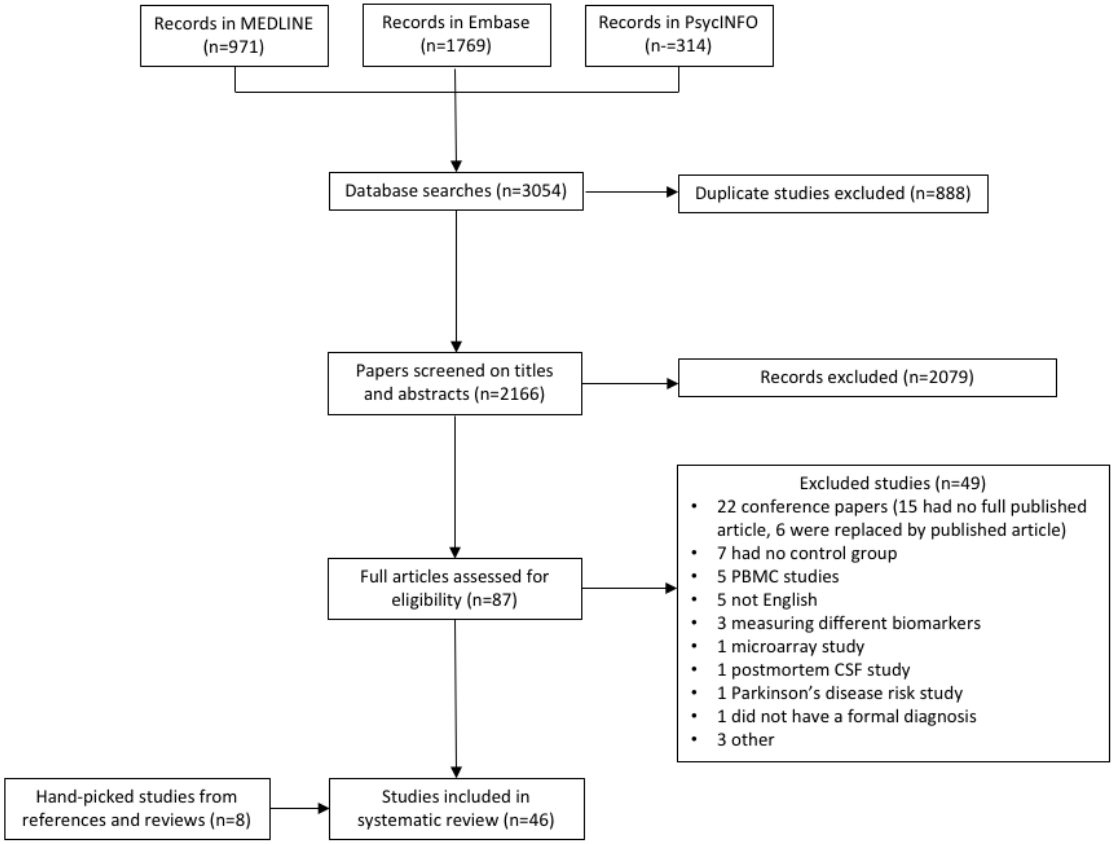

Figure 1: Flow chart of studies through screening

Table 1

Study	Number of participants	Disease Duration (years)	Age (years)	Method used	Pro-inflammatory								Variable		Anti-inflammatory	
					IL-1alpha	IL-1beta	IL-2	IL-8	IL-12	IL-15	TNF-alpha	INF-gamma	IL-6	TGF-beta1	IL-4	IL-10
Pirttila 1994 (14)	20 PD 42 Controls	New onset	PD: 64.6 control: 60.9	ELISA		NS										
Hu 2015 (36)	210 PD 31 Control	2.3	PD: 60.2 Control: Matched	ELISA		↑***					NS					
Hu 2015 (37)	225 PD 31 Controls	2.2	PD:59.0 Control: Matched	ELISA		↑***					↑*					
Koziorowski 2012 (18)	60 PD 24 Controls	11.2	PD: 59.2 Control: 64.0	cytokine multiplex kit		NS		NS	NS		↑***		NS			NS
Williams-Gray 2016 (40)	230 PD 93 Controls	0.6	PD: 66.4 Control:68	MSD		↑***	↑***	NS	NS		↑***	NS	NS			↑***
Dursun 2015 (35)	40 PD 32 Controls	Not specified	PD: 71.0 Control: 72.1	ELISA	↓*	↑**							↓***			
Blum-Degen 1995 (19)	22 PD 12 Controls	0.5-3.0	PD: 61.0 Control: 61.0	ELISA		NS	NS						NS			
Brockmann 2016 (38)	144 iPD, 142 PD LRRK2 133 Controls	7 10.5	iPD: 68.5 PD LRRK2: 66.0 Control: 57.5	Multiplexed immunoassay		↑* NS		{↓*} NS	↑**(*) (↑*)		NS NS		{↑*} (↑**)		NS NS	↑*** NS

Rota 2006 (29)	14 PD 25 Controls	3.0	PD: 66 Control: 69	ELISA					NS		ND		NS		NS	
	10 PDD	7.2	PDD: 69	ELISA					NS		ND		NS		NS	
Da silva et al 2015 (41)	21 PD 21 Controls	6.0	PD: 59.0 Control: 59.0	Cytometric bead array		NS		NS		NS			NS			
Zakarya 2004 (28)	30 PD 20 Controls	Not specified	PD: 65.4 Control: Matched	ELISA		↑***		↑***		↑***			↑***			
Stypula 1996 (15)	21 PD 25 Controls	Recent onset	PD: 64.6 Control: Matched	RIA	↑**		NS						NS			
Gupta 2016 (39)	81 PD 83 Controls	3.2	PD: 58.5 Control: 57.6	ELISA				↓***		↓***						
Brodacki 2008 (30)	31 PD 20 Controls	6.9	PD:61.5 Control:67.0	Cytometric bead array			↑**			↑**	↑**		↑**		↑**	↑**
Gruden 2012 (34)	32 PD 26 Control	1-5	PD: 60.8 Control: 63.0	ELISA					↑(153%)	↓(100%)	↑(444%)					
Lindqvist 2012 (52)	86PD 40 Controls	6.9	PD: 64.2 Control: 64.8	Chemoiluminescent assays						NS			↑*			
Dobbs 1999 (26)	78 PD 140 Controls	Not specified	PD: 69.4 Control: 61.4	ELISA						NS			NS			

Scalzo 2009 (32)	46 PD 23 Controls	7.5	PD: 65.8 Control: 61.9	ELISA							NS					
Scalzo 2010 (33)	44 PD 22 Controls	7.4	PD: 65.7 Control: Matched	ELISA									↑*			
Tang 2014 (13)	78 PD 80 Controls	5.5	PD: 76.3 Control:75.4	ELISA									↑**			
Hofmann 2009 (31)	23 PD+LDopa 17 Untreated 23 Controls	8.1 2.8	PD+LDopa:66.5 Untreated: 65.3 Control:60	ELISA									NS NS			
Selikhova 2001 (42)	45 PD 15 Controls	Not specified	PD: 68.2 Control: 62.5	ELISA									NS			
Varani 2010 (43)	56PD 60 Controls	5.5	PD: 74.2 Control: 71.4	ELISA							↑**					
Choi 2008 (11)	8 PD 13 Controls	De novo	PD: 73.0 Control: 68.5	Luminex xMAP	NS	ND	ND	NS	NS	ND	NS	NS	ND		NS	ND
Rentzos 2007 (22) & Rentos 2009 (23)	41 PD 19 Controls	4	PD: 67.5 Control: 65.8	ELISA					NS	NS						↑**
Fattah 2011 (12)	30 PD 20 Controls	10	PD: 48.0 Control: 47.1	ELISA						↑**						NS

Gangemi (27)	2003	12 PD+Ldopa 12 untreated 12 Controls	7 2.2	L-Dopa: 65.2 Untreated: 58.4 Control: matched	ELISA	↑* NS	

Table 1: All studies investigating cytokine levels in peripheral blood whereby authors in italics used plasma and all other authors used serum. It is indicated whether there is a significant increase or decrease, where * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, NS = non-significant and ND = cytokine not detected. ELISA = Enzyme-linked immunosorbent assay, MSD = Meso Scale Discovery, RIA = Radioimmunoassay. iPD = idiopathic PD patients, LRRK2 PD = patients with the LRRK2 mutation. LDopa = patients receiving levodopa medication, only used when the PD group is split into those who are receiving treatment and those who are not. () = males only, {} = females only. Studies highlighted in grey indicate LBD, all other studies investigate PD only.

Table 2

Study	Number of participants	Disease duration (years)	Age (years)	Method used	Pro-inflammatory							Variable		Anti-inflammatory	
					IL-1alpha	IL-1beta	IL-2	IL-8	IL-12	TNF-alpha	INF-gamma	IL-6	TGF-beta1	IL-4	IL-10
Martin de Pablos 2015 (48)	29 PD 21 controls	Not specified	PD: 63.4 controls:67.9	ELISA (lumbar)									↑**		
Mogi 1995 (24) & Mogi 1996 (25)	14 PD 13 control	Not specified	PD: 68.0 Control:46.0	ELISA (ventricular)		NS	↑*					↑*	↑**	NS	
Rota 2006 (29)	14 PD 25 Controls	3.0	PD: 66.0 Control: 69.0	ELISA					NS				NS		NS
	10 PDD	7.2	PDD: 69.0	ELISA					NS				NS		NS
Hu 2015 (36)	225 PD 31 control	2.2	PD: 59.0 Control: Matched	ELISA (lumbar)		↑*				NS					
Hu 2015 (37)	210 PD 31 control	2.3	60.2 Control: Matched	ELISA (lumbar)		↑*** (PRBD)				NS					
Blum-Degen 1995 (19)	22 PD 12 Control	0.5-3.0	PD: 61.0 Control: 61.0	ELISA (lumbar)		↑*	NS					↑*			
Pirttila 1994 (14)	20 PD 42 control	New onset	PD: 64.6 control: 60.9	ELISA (lumbar)		NS									
Mogi 1994 (44)	15 PD 16 controls	Not specified	PD: 58 Control: 46	Sandwich EIA (lumbar)						↑**					

Muller 1998 (45)	22 PD 44 controls	Not specified	PD: 61.0 Control: Matched	ELISA (lumbar)								↑*		
Yu 2014 (46)	26 PD 31 controls	2.0	PD: 57.4 Controls: 52.2	ELISA (lumbar)		↑*				NS	↓*	NS		
	3 PDD 33 PD-MCI	3.0	PD-CI:61.1	ELISA (lumbar)		↑***				↓**	↓**	↑*		
lindvquist 2013 (17)	71 PD 33 control	PD:6.4	PD: 64.2 Control: 65.8	MSD (lumbar)						NS		NS		
	16 PDD	15.8	PDD: 70.0	MSD (lumbar)						NS		NS		
Janelidze 2015 (47)	82 PD 38 control	6.5	PD: 64.5 Control: 65.4	ELISA (lumbar)				NS						
	18 PDD	16.3	PDD: 72.3	ELISA (lumbar)				↑*						
Wennstrom 2015 (6)	29 DLB 36 control	Not specified	DLB: 74.0 Control: 62.0	MSD (lumbar)								↓**		
Gomez-Tortosa 2003 (49)	25 DLB 46 control	2.25	DLB: 75.2 Controls: 72.7	ELISA (lumbar)		NS						NS		
Choi 2008 (11)	8 PD 13 Control	De novo	PD: 73.0 Control: 68.5	Luminex xMAP	NS	ND	ND	ND		ND	ND	ND	ND	ND

Table 2: All studies investigating cytokine levels in CSF. It is indicated whether there is a significant increase or decrease, where * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, NS = non-significant and ND = cytokine not detected. ELISA = Enzyme-linked immunosorbent assay, EIA =

Enzyme Immunoassay, MSD = Meso Scale Discovery. (PRBD) = Probable REM sleep behavioural disorder patients only. Studies highlighted in grey indicate LBD, all other studies investigate PD only.

Table 3

Study	Biofluid	Number of participants	Disease duration (years)	Age (years)	CRP vs control
Akil 2015 (54)	Blood	51 PD 50 controls	6.1	PD: 69.5 Control:65.9	↑**
Andican 2012 (51)	Blood	45 PD 25 controls	6.4	PD: 63.6 Controls:60.2	NS
Lindqvist 2012 (52)	Blood	86 PD 40 controls	6.9	PD: 64.2 Controls: 64.8	NS
Lindqvist 2013 (17)	CSF	71 PD 33 control	6.4	PD: 64.2 Control: 65.8	NS
		16 PDD	15.8	PDD: 70.0	↑*
Sawada 2014 (53)	Blood	111 PD 53 controls	8.0	PD: 69.7 Control: 69.1	NS
Song 2009 (20)	Blood	212 PD 119 controls	2.1	PD: 68.7 Controls: 66.6	↑**
Song 2011 (21)	Blood	63 PD 117 controls	1.0	PD: 63.7 Controls: 66.6	↑**

Song 2013 (16)	Blood	72 PD 84 control	SYMPTOM duration 1.6	PD: 69.7 controls:73.2	↑***
		45 PDD	1.9	PDD:71.4	↑***
Song 2014 (10)	Blood	435 PD 221 controls	SYMPTOM duration 2.3	PD: 69.4 controls: 68.5	↑***
Umemura 2015 (55)	Blood	375 PD 65 controls	6.6	PD: 69.3 Control: 63	↑**
Williams-Gray 2016 (40)	Blood	230 PD 93 controls	0.6	PD: 66.4 controls: 68.0	NS

Table 3: All studies investigating CRP levels. It is indicated whether there is a significant increase or decrease, where * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ and NS = non-significant.